UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,988	07/07/2004	Url Meir	26235	3129

20529 7590 12/16/2009

THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314

EXAMINER	
SAUCIER, SANDRA E	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
12/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,988	MEIR, URL	
	Examiner	Art Unit	
	Sandra Saucier	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78,98-115 and 119-123* is/are pending in the application.

4a) Of the above claim(s) *111-113* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78,98-110,115 and 119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 78, 98-115, 119-123 are pending. Applicants have elected "semen" as the species under examination. Therefor claims 111-113 have been withdrawn and claims 78, 98-110, 115, 119-123 are under examination.

Claim Rejections - 35 USC § 112

Claims 78, 98-110, 115, 119-123 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the freezing of semen from different species with a cryoprotectant, does not reasonably provide enablement for the freezing any biological matter, particularly with no cryoprotectant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The invention is in the field of cryopreservation of biological matter, elected species of semen, for future medical/veterinary use.

The working examples are all directed to the freezing/thawing of suspension of sperm in extenders which contain glycerol, glucose, egg yolk etc..

The claims encompass the freezing of any biological matter including semen, blood, blood cells, blood constituents and umbilical cord blood cells without cryopreservatives.

The state of the art is as follows.

Freezing technology with regard to biological materials is an empirical art with centuries of experimentation.

While the instant claims do not require any cryopreservative, the art of freezing cells without cryopreservatives is non-existent except in the food art. However, freezing food is distinct from the instant application where the frozen material is to be employed in medical procedures such as IVF, transplantation

and other medically related purposes. The criteria for a successful freezing/thawing protocol of a frozen dinner is much lower than for a blood cell intended for transfusion, for example.

Also, the type of cryopreservative for a particular cell type is also critical and is an area of unpredictability. The type and concentration of cryopreservative is derived empirically, see Guillouzo *et al.* [U2] where for one cell type, hepatocytes, critical parameters are the choice of the cryoprotectant and the composition of the freezing medium (abstract). On page 9, it is disclosed that even the species of animal from which the hepatocytes are derived requires changes in the freezing medium composition for best results.

In short, freezing of cells is still an art with great unpredictability in terms of successful freezing of even the various types of single cells in suspension, coupled with the unpredictability of the concentrations and types of cryoprotectants for each cell type.

Undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

DECLARATION of P. PATRIZIO

The declaration of P. Patrizio under 37 CFR 1.132 filed 11/6/08 is insufficient to overcome the rejection of claims 78, 98-115, 119-123 based upon 35 USC §112, first paragraph as set forth in the last Office action because: no objective evidence has been presented. P. Patrizio's opinion is that the specification provides sufficient description for a skilled artisan to make and use a method of freezing at least semen without the necessity of including a cryoprotectant, and that one of ordinary skill in the art knows that freezing of semen from different species is possible without the inclusion of a cryoprotectant.

It is recognized that one can freeze anything without a cryoprotectant such as muscle tissue (steak) or pancreas (sweetbreads) or even brain and the thawed product would be suitable for use as food. However, the question is whether the thawed muscle tissue or pancreas or brain, frozen under such conditions is useful in the medical field for grafting as taught in the specification on page 1.

The declaration is directed primarily to the freezing of semen, but the claims are not limited to the freezing of semen. Therefore, the declaration is not commensurate in scope with the claim language and cannot be persuasive of the enablement of the instant claims. The declaration does not present any objective evidence such as a published article, that even sperm/semen can be frozen without a cryoprotectant and thawed with retention of function. The examples of the instant specification show only the freezing and thawing of semen/sperm with glycerol. Thus, neither the declaration not the specification objectively demonstrate the scope of the claimed method, and there does not appear to exist a body of knowledge in the field of medical technology which would support the scope of the instant claims.

ATTACHMENT A in the reply of 6/29/09

Attachment A is not in the form of a declaration, thus it is uncertain what patentable weight should be given the data submitted. Applicants continue to allege that no cryoprotectant is necessary to successfully practice the claimed freezing protocol. Success in the context of this application, means with sufficient retention of biological function to permit the use of the frozen biological matter for medical purposes. In an attempt to substantiate this point, applicants present in Attachment A, section 2.2 an experiment which supposedly illustrates the freezing of large volumes of umbilical cord blood cells with and without cryoprotectant. One sample was frozen with trehalose and EGCG, which presumably means epigallocatechin gallate, an antioxidant found in green tea among other sources. This is what applicant's allege is the sample with no cryoprotectant. Please note that trehalose is a well known cryoprotectant, see Buchanan *et al*. [U]. Example 1 of the attachment A shows

the freezing of red blood cells in Dextran 40, which is a cryoprotectant and epigallocatechin. Example 2.1 uses DMSO as the cryoprotectant, example 3 again uses DMSO or trehalose as the cryoprotectants. Once again, it has been demonstrated that contrary to the declaration of P. Patrizio, freezing biological samples in the absence of cryoprotectants with retention of medical/biological function is not known in the art of cryopreservation and has not been demonstrated by applicants. Thus, the claimed method is not enabled.

The examiner has indicated that the specification is considered to be enabling for the freezing of semen/sperm with the inclusion of a semen extender containing glycerol. In example 1 of the specification, AndroMed® which contains glycerol is used, in example 2, an extender containing glycerol was used, in example 3, glycerol was used, in example 4, glycerol was used, example 5, New Zealand® extender was used and it is assumed that glycerol was the cryoprotectant. However, the claims are not so limited and therefore continue to be rejected for lack of enablement.

Applicant argues in the paper of 11/6/08 that they have met the written description requirement. However, the rejection is a scope of enablement rejection not a written description rejection. Written description is separate and distinct from the enablement requirement, see MPEP 2164 and in particular 2164.03. Thus, the arguments are not persuasive of error in the rejection since the examiner has provided a quantity of objective evidence of unpredictability in the art of freezing biological material for the disclosed purpose in the specification, which objective evidence has not been persuasively rebutted by applicant.

Response to Arguments of 6/29/09

While the specification may be enabling for certain embodiments, as stated by the examiner above, THE CLAIMED METHOD IS NOT ENABLED. The claimed method does not require a cryoprotectant, which the examiner has shown is a critical element, without which success in the practice of the claimed method is not reasonably expected to be successfully performed, as fully explained above. If applicant wishes to claim a method which rebuts the

objective evidence presented by the examiner and even by the applicant, himself, such a method must be demonstrated, particularly in a field which has been shown to be an empirical field with many failures, *i.e.* unpredictable. It is noted that applicant has not submitted any peer-reviewed references describing a freezing method for medical/veterinary purposes which do not include a cryoprotectant in the sample. If applicant has discovered such a freezing method which does not require a cryoprotectant, it has not been demonstrated. The method AS CLAIMED is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 78, 98-100, 102, 106, 114, 123 are rejected under 35 U.S.C. 102(a) as being anticipated by Arav *et al.* [U] in light of the Baxter Catalog [V].

Arav *et al.* disclose the method of freezing a whole ejaculate in a 12 ml test tube. The freezing method is by the method disclosed in US 5,873,254 as cited on page 584 of the reference and incorporated thereby into the reference of Arav *et al.*. In the particular example of Arav *et al.*, the sample moves through a temperature gradient at a constant velocity. This reference also points to the criticality of the velocity of movement of a sample through the temperature gradient, see Figure 2.

Test tubes which can contain 12 mls come in standard sizes with diameters of 13 mm, 16mm, 19mm and so forth. Thus, the smallest diameter of a test tube which can contain 12 mls is 13mm which is larger than 0.5cm in two perpendicular directions, see Baxter Catalog.

Claim Rejections - 35 USC § 103

Claims 78, 98-110, 114, 115, 119-123 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,873,254 [IDS].

The claims are directed to a method for changing the temperature of a sample comprising:
(i) changing the temperature of the sample by subjecting it to a temperature gradient from an initial to an intermediate temperature,
(ii) subjecting the sample to the intermediate temperature until the sample uniformly reaches the intermediate temperature,
(iii) changing the temperature of the sample until it reaches a final temperature,
wherein the sample exceeds 0.5 cm in at least two mutually perpendicular cross sections and wherein the initial, intermediate and final temperatures are different and all progress in either a higher or lower sequence from one another.

US 5,873,254 teaches a method of changing the temperature of a sample comprising: subjecting the sample to a temperature gradient to change the temperature of the sample from an initial temperature to an intermediate temperature, held at the constant intermediate temperature, then changing to a final temperature (col. 5, ls. 40-60, col. 6). The temperature is a constant -7C as the sample moves through block 14. This corresponds to maintaining the temperature by pausing the sample. Whether the temperature is maintained at an intermediate level by pausing the sled or having the block uniformly the same intermediate temperature as the sled moves through appears to be an element of experimental design because the result is the same, i.e. maintenance of the same temperature in the sample for a period of time. This reference teaches a freezing method based on directional freezing as the material is moved through a temperature gradient so that the cooling rate and ice propagation front are precisely controlled, instead of the more familiar and common multi-directional heat transfer methods.

The reference lacks the explicit stipulation of the size of the sample as exceeding 0.5cm in each of two mutually perpendicular cross-sections.

In the generic description of the invention (Summary of Invention), no limitation as to the size of the sample is described. Thus, the generic description is non-limiting with regard to size of sample.

While the size of the sample in the exemplification is ABOUT 1cm X 1cm x 0.5mm (col. 6, l. 15), use of the term "about" permits a variation of undefined range around this measurement. Also, please see MPEP 2144 IV A where it is stated that changes in size, shape or sequence of adding ingredients is *prima facie* obvious. Mere scaling up of a prior art process including an apparatus use to perform the process is not sufficient to patentably distinguish over the art in the absence of other evidence.

Claims 78, 98-110, 114, 115, 119-123 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,873,254 [IDS] in combination with US 4,131,200 [A] in light of Dayian *et al.* [V2].

The claims and US 5,873,254 have been discussed above. Also, please note that no dimensions have been stipulated which might limit the size of the apparatus and no negative limitations have been used to limit the size of the samples used in the controlled freezing method of US '254. Semen is a biological sample which has been expressly mentioned in col. 1, l. 3 of US '254.

US 4,131,200 discloses a bag designed for freezing biological materials such as platelets. The dimensions of the bag are 9.3 cm by 10.2 cm. The method of Dayian *et al.* was used to test the bags. Dayian *et al.* teach a PC concentration of about 57 mls, see footnote on Table 1A. A calculation of the thickness of the bag when containing a volume of 57 mls is 57 cc = 9.3cm x 10.2 cm x Thickness. Solving for T = about 0.6 cm.

Therefore, the substitution of the controlled freezing method of laterally varying thermal gradients for biological cells such as semen for the uncontrolled freezing method described in US 4,131,200 would have been obvious for the advantages taught in US 5,873,254, such as improved viability of cells.

Claims 78, 98-110, 114, 115, 119-123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arav *et al.* [U] in combination with US 5,873,254 [IDS] in light of Swanson *et al.* [W] and the Baxter Catalog [V].

Arav *et al.* disclose the method of freezing a whole ejaculate in a 12 ml test tube. The freezing method is by the method disclosed in US 5,873,254 as cited on page 584 of the reference and incorporated thereby into the reference of Arav *et al.*. In the particular example of Arav *et al.*, the sample moves through a temperature gradient at a constant velocity. This reference also points to the criticality of the velocity of movement of a sample through the temperature gradient, see Figure 2.

US 5,873,254 has been described above.

Swanson *et al.* disclose that the volume of a whole bull ejaculate averages about 4.5 ml, Tables 1 and 2 and may be up to 11mls in volume.

The Baxter Catalog information on standard tube sizes has been discussed above.

The use of the multithermal gradient directional cooling device and methods described in US '254 with the semen sample of Arav *et al.* would have been obvious particularly because Arav *et al.* state that the Multi-thermal gradient technology (MTG®) which is disclosed in US '254 is used to demonstrate the freezing of large samples such as a whole ejaculate from a bull.

US '254 describes the process of directional control of the freezing process by moving the sample through a first cooling gradient from 22°C to 0°C, then into a constant temperature area of -7°C, with seeding of the ice front using liquid nitrogen and then into another temperature gradient of -10 to -35°C. Also, the sample is maintained constant @-7°C for a period of time, see col. 6, lines 27-65.

Therefore, it would have been obvious to freeze the semen sample of Arav *et al.*, which can vary from about 4.5 mls on average to up to 11 mls using this process of multigradient directional cooling, including using any velocity, thermal gradient, pausing at a constant temperaure for a desired period of time, particularly since all these maneuvers are taught in US '254.

With regard to the freezing of sample with volumes of greater than 12 mls or greater than 50mls or more, which includes an infinite volume, which does not appear to be a reasonable upper limit since an infinite volume of semen would require an infinitely large apparatus and semen obtained from an infinite number of males, one of skill in the art may increase the size of samples and apparatus as desired.

One of ordinary skill in the art would have been motivated at the time of invention to make these substitutions/variations in order to obtain the results as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

DECLARATION OF A. Arav

The declaration of A. Arav under 37 CFR 1.132 filed 11/6/08 is insufficient to overcome the rejection of claims 78, 98-115, 119-123 based upon 35 USC § 103 over US '254 as set forth in the last Office action.

A. Arav states that US '254 describes a device which is capable of producing a uniform cooling rate of -0.1°C/min through a biological sample and also describes method for the freezing of semen involving cooling the semen sample from 30°C to an "intermediate temperature" which is slightly below the lipid phase transition temperature at a rate slow enough to prevent chilling injury, preferably about 1°C/min. A. Arav states that the sample size described in US '254 refers to a smaller sample size than the present sample in the instant claims. The sample size described in the exemplification of US '254 is "about 1 cm X 1 cm X 0.5mm"; however, the generic description of the method and the device used in the method are without size or dimension limitations, nor are they any teachings in the reference with regard to size limitations. Thus, while the exemplified sample size may be less than the instantly claimed sample size, this is not significantly persuasive to overcome an obviousness rejection, particularly since scaling up is *prima facie* obvious.

A. Arav states that it is his belief and understanding that the bulk of the sample being frozen is crucial and has a great effect on post thaw viability. The larger the sample the more damage it suffers. This is a function of the heat transfer properties. While this may be true, the method of the prior art reference US '254 discloses a zone of constant temperature -7°C in which the sample remains for about 10 minutes (col. 6, l. 64). The instant exemplification has a zone of constant temperature (a pause) in example 3 which is for 20 seconds and example 4, for 60 seconds. Clearly a pause of 10 minutes, which is the time period of constant intermediate temperature taught in the prior art reference would permit equilibration of the temperature in the sample as in the instant method because the time of the pause at a constant intermediate temperature is greater than the pauses (constant temperature periods) demonstrated in the instant exemplifications. Mere rephrasing or realization of concepts already taught by specific examples in the prior art is not sufficient to overcome a prior art rejection.

Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. See Titanium Metals, 778 F.2d at 780. Artisans of

ordinary skill may not recognize the inherent characteristics or functioning of the prior art. See id. at 782. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.

"The public remains free to make, use, or sell prior art... processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle." See Atlas Powder Co. v. IRECO Inc. 51 USPQ2d 1943 (Fed. Cir. 1999).

While applicant has demonstrated a method for freezing larger volume semen/sperm samples with glycerol and may have presented some unexpected results, the claims are not directed to such a method and the arguments are not directed to the results presented.

Response to Arguments

Applicant's arguments filed 2/26/08 have been fully considered but they are not persuasive. Previous rebuttals may be found in the previous office actions and are not repeated.

Applicant argues that in small samples, the outer and inner zones change their temperatures essentially at the same rate and that the cited prior art does not teach subjecting the sample to an intermediate temperature until the temperature of the sample in the cross-section is uniform and equals the intermediate temperature, and thus, the presently claimed method is not a mere scaling up of the prior art method.

Please note that "essentially the same rate" is not the same rate. Essentially the same is a relative term, which only means that the rate is not the same. If a temperature change is applied from the outside of a sample, the inner temperature will equilibrate with the outer temperature at a rate which is limited by the heat transfer rate of the sample. This is true no matter what the

size of the sample. This is due the thermodynamics of heat transfer during conduction and is dependent on the thermal conductivity of the sample, k=Q/t times L/A x ΔT, where k is the thermal conductivity constant, Q is the quantity of heat, t is the time, L is the thickness, A is the surface area and ΔT is the change in temperature. Please notice that all samples have thickness, therefore have positive rates of heat transfer. Only if the sample has no dimensions is heat transfer infinitely large and therefore, truly instantaneous or "the same".

With regard to the "pausing" of the sample at one temperature or uniformity of temperature in the sample, please see col. 6, l. 64 of the prior art reference where the sample spends about 10 minutes inside block 14 at constant temperature of -7°C, then decreases the temperature again to-35°C at a rate of 0.3°C/min. This appears to be a pausing at an intermediate temperature which according to applicant's arguments concerning heat transfer rates, would reasonably be enough time to equilibrate the sample in any cross-section. Also, in applicants arguments on page 15, applicant states that uniformity may be achieved by methods (a), (b) or (c). It appears that method (c) was exemplified in col. 6, l. 64 of the prior art reference.

Applicant argues in the response of 11/6/08 that the instant claims are not merely scaling up the prior art method and that unexpectedly superior results are achieved with the presently claim subject matter. Applicants then further state the presently claimed subject matter is directed to a method for the cryopreservation of relatively large semen samples. Please note that applicant's arguments are not commensurate in scope with their claims or the alleged superior results which are purported to have been demonstrated in the specification.

Arguments concerning the teachings of US '254 with regard to "intermediate temperature" equilibration vs. the CLAIMED method have been answered above in the response to A. Avav's declaration and in the response to arguments mailed 5/6/08. It is the examiner's carefully considered opinion that the instant claims have not overcome the cited prior art reference of US

'254 which teaches the general method of decreasing the temperature of a sample using a temperature gradient, holding the sample at one temperature for the exemplified 10 minutes (col. 6, l. 64) and continuing to lower the temperature of the sample to a final temperature.

Applicant argues in the response of 6/29/09 that a proper case of *prima facie* obviousness has not been established because all the element of the claims are neither taught nor suggested by US '254. Applicants argue that a method for changing the temperature of a biological sample (semen) having a minimal dimension in each of two mutually perpendicular cross-sections that exceeds 0.5 cm. While it may be correct that this phraseology is not exactly replicated in the references, the facts remain that 1) the generic disclosure of the apparatus and method of use of the apparatus in US '254 have no size or volume limitations. MPEP 2144 IV. A. clearly states that a *prima facie* case of obviousness exists when changes in size or mere scaling up of prior art disclosure is the difference upon which patentability depends; and 2) the element of size of the sample, is found in the prior art disclosure of US ''200, where a sample which has been shown to in fact have a minimal dimension in each of two mutually perpendicular cross-sections that exceeds 0.5 cm and it has been frozen for medical use in a different protocol. Also, in the newly cited reference of Arav *et al.*, a clear teaching of the use of the protocols and apparatus of US'254 has been exemplified with a sample which in fact has a minimal dimension in each of two mutually perpendicular cross-sections that exceeds 0.5 cm. Merely because the exact words of the claim are not repeated does not mean that the reference does not apply when the element which is in the claim and argued to be the distinguishing element is disclosed as inherent fact, that is the sample size is larger than the dimensions which are in the claim. Also, changes in dimension of the sample or apparatus are not sufficient in themselves to overcome a reference which teaches the same essential steps in the freezing protocol.

Applicant argues that the freezing method described in US '254 is different from the presently claimed method. The question is not if it is

different, but if it is obvious over the disclosed freezing protocols. Since, the methods disclosed and the methods claimed all use protocols of cooling a sample in a first gradient (22C to 0°C, exemplified in US '254), seeding crystal propagation with liquid nitrogen, which propagation moves in one direction, holding the temperature of the sample constant (US '254 exemplified -7°C) and again cooling the sample in a second gradient (-10°C to -35°C, exemplified in US '254). It is the still the examiner's position that the claimed methods are obvious over the cited references.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the

Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
Primary Examiner
Art Unit 1651